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=> d his

     (FILE 'HOME' ENTERED AT 16:30:03 ON 24 SEP 2007)

     FILE 'REGISTRY' ENTERED AT 16:31:43 ON 24 SEP 2007
                E CADPR/CN
L1            1 S E3

     FILE 'CAPLUS, MEDLINE' ENTERED AT 16:32:39 ON 24 SEP 2007
L2         1130 S L1
L3           30 S L2 AND INFLAMM?
L4         1100 S L2 NOT L3
L5            8 S L4 AND ASTHMA?
L6            0 S L4 AND SEPSIS?
L7            0 S L4 AND HEMORR?
L8            0 S L4 AND ENDOTOX?
L9            0 S L4 AND PANCREATIT?
L10           0 S L4 AND CROHN?
L11           0 S L4 AND ULCER?
L12           0 S L4 AND PHOSPHOROTHI?
L13           0 S L4 AND PHOSPHOROAMID?
L14          33 S L4 AND CADPR ANALOG?
L15           0 S L14 AND INFLAMM?
L16           0 S L4 AND INTESTINAL EPITHEL?
L17           0 S L4 AND COLITIS?
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     (FILE 'HOME' ENTERED AT 16:30:03 ON 24 SEP 2007)

     FILE 'REGISTRY' ENTERED AT 16:31:43 ON 24 SEP 2007
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L1             1 S E3

     FILE 'CAPLUS, MEDLINE' ENTERED AT 16:32:39 ON 24 SEP 2007
L2          1130 S L1
L3            30 S L2 AND INFLAMM?
L4          1100 S L2 NOT L3
L5             8 S L4 AND ASTHMA?
L6             0 S L4 AND SEPSIS?
L7             0 S L4 AND HEMORR?
L8             0 S L4 AND ENDOTOX?
L9             0 S L4 AND PANCREATIT?
L10            0 S L4 AND CROHN?
L11            0 S L4 AND ULCER?
L12            0 S L4 AND PHOSPHOROTHI?
L13            0 S L4 AND PHOSPHOROAMID?
L14           33 S L4 AND CADPR ANALOG?
L15            0 S L14 AND INFLAMM?
L16            0 S L4 AND INTESTINAL EPITHEL?
L17            0 S L4 AND COLITIS?
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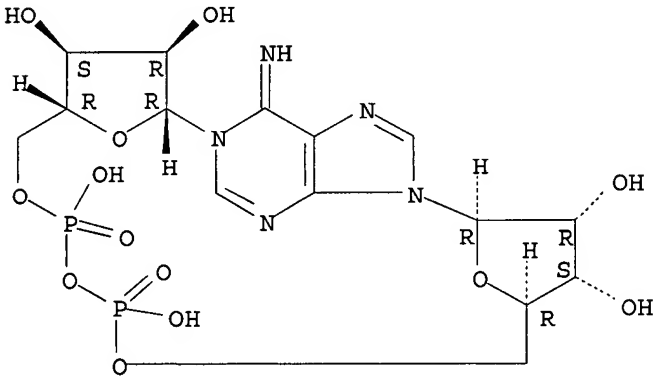
L1 ANSWER 1 OF 1 REGISTRY COPYRIGHT 2007 ACS on STN
RN 119340-53-3 REGISTRY
ED Entered STN: 03 Mar 1989
CN Adenosine 5'-(trihydrogen diphosphate), 1-β-D-ribofuranosyl-, intramol. P',5''-ester (CA INDEX NAME)
OTHER NAMES:
CN cADPR
CN cAPD ribosè
CN Cyclic ADP-ribose
FS STEREOSEARCH
DR 143822-66-6, 150155-83-2
MF C15 H21 N5 O13 P2
CI COM
SR CA
LC STN Files: AGRICOLA, ANABSTR, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CSCHEM, EMBASE, MEDLINE, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

593 REFERENCES IN FILE CA (1907 TO DATE)
20 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
594 REFERENCES IN FILE CAPLUS (1907 TO DATE)

L3 ANSWER 20 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006754250 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17191385
TITLE: CD38: an ecto-enzyme at the crossroads of innate and adaptive immune responses.
AUTHOR: Partida-Sanchez Santiago; Rivero-Nava Laura; Shi Guixiu; Lund Frances E
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY 12983, USA.
CONTRACT NUMBER: AI-057996 (NIAID)
AI-43629 (NIAID)
SOURCE: Advances in experimental medicine and biology, (2007) Vol. 590, pp. 171-83. Ref: 39
Journal code: 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
General Review; (REVIEW)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200702
ENTRY DATE: Entered STN: 29 Dec 2006
Last Updated on STN: 28 Feb 2007
Entered Medline: 27 Feb 2007

L3 ANSWER 21 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006562563 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16987244
TITLE: Cyclic ADP-ribose is a second messenger in the lipopolysaccharide-stimulated activation of murine N9 microglial cell line.
AUTHOR: Franco Luisa; Bodrato Nicoletta; Moreschi Iliana; Usai Cesare; Bruzzone Santina; Scarf i Sonia; Zocchi Elena; De Flora Antonio
CORPORATE SOURCE: Department of Experimental Medicine, Section of Biochemistry, and Center of Excellence for Biomedical Research, University of Genova, Genova, Italy.
SOURCE: Journal of neurochemistry, (2006 Oct) Vol. 99, No. 1, pp. 165-76.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200611
ENTRY DATE: Entered STN: 22 Sep 2006
Last Updated on STN: 15 Nov 2006
Entered Medline: 14 Nov 2006

AB Lipopolysaccharide, the main component of the cell wall of Gram-negative bacteria, is known to activate microglial cells following its interaction with the CD14/Toll-like receptor complex (TLR-4). The activation pathway triggered by lipopolysaccharide in microglia involves enhanced basal levels of intracellular calcium ([Ca2+]i) and terminates with increased generation of cytokines/chemokines and nitric oxide. Here we demonstrate that in lipopolysaccharide-stimulated murine N9 microglial cells, cyclic ADP-ribose, a universal and potent Ca2+ mobiliser generated from NAD+ by ADP-ribosyl cyclases (ADPRC), behaves as a second messenger in the cell activation pathway. Lipopolysaccharide induced phosphorylation, mediated by multiple protein kinases, of the mammalian ADPRC CD38, which resulted in significantly enhanced ADPRC activity and in a 1.7-fold increase in the concentration of intracellular cyclic ADP-ribose. This event was paralleled by doubling of the basal [Ca2+]i levels, which was largely

prevented by the cyclic ADP-ribose antagonists 8-Br-cyclic ADP-ribose and ryanodine (by 75% and 88%, respectively). Both antagonists inhibited, although incompletely, functional events downstream of the lipopolysaccharide-induced microglia-activating pathway, i.e. expression of inducible nitric oxide synthase, overproduction and release of nitric oxide and of tumor necrosis factor alpha. The identification of cyclic ADP-ribose as a key signal metabolite in the complex cascade of events triggered by lipopolysaccharide and eventually leading to enhanced generation of pro-inflammatory molecules may suggest a new therapeutic target for treatment of neurodegenerative diseases related to microglia activation.

L3 ANSWER 22 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006272844 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16547971
TITLE: CCL5 evokes calcium signals in microglia through a kinase-, phosphoinositide-, and nucleotide-dependent mechanism.
AUTHOR: Shideman C R; Hu S; Peterson P K; Thayer S A
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota, Minneapolis, Minnesota, USA.
CONTRACT NUMBER: DA04381 (NIDA)
DA07304 (NIDA)
DA09924 (NIDA)
DA11806 (NIDA)
SOURCE: Journal of neuroscience research, (2006 Jun) Vol. 83, No. 8, pp. 1471-84.
Journal code: 7600111. ISSN: 0360-4012.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, N.I.H., EXTRAMURAL)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200609
ENTRY DATE: Entered STN: 17 May 2006
Last Updated on STN: 9 Sep 2006
Entered Medline: 8 Sep 2006

AB Microglia, the resident macrophages of the CNS, are responsible for the innate immune response in the brain and participate in the pathogenesis of certain neurodegenerative disorders. Chemokines initiate activation and migration of microglia. The beta-chemokine CCL5 induces an elevation in intracellular calcium concentration ([Ca(2+)](i)) in human microglia. Here, we examined the signal transduction pathway linking activation of chemokine receptor CCR5 to an elevation in [Ca(2+)](i) in cultured microglia by using pharmacological approaches in combination with Fura-2-based digital imaging. The CCL5-induced response required Janus kinase (Jak) activity and the stimulation of an inhibitory G protein. Multiple downstream signaling pathways were involved, including phosphatidylinositol 3-kinase (PI3K), Bruton's tyrosine kinase (Btk), and phospholipase C (PLC)-mediated release of Ca(2+) from inositol 1,4,5-trisphosphate (IP(3))-sensitive stores. Activation of both the kinase and the lipase pathways was required for eliciting the Ca(2+) response. However, the majority of the [Ca(2+)](i) increase was derived from sources activated by NAD metabolites. Cyclic ADP-ribose (cADPR) evoked Ca(2+) release from intracellular stores, and ADPR evoked Ca(2+) influx via a nimodipine-sensitive channel. Thus, a multistep cascade couples CCR5 activation to Ca(2+) increases in human microglia. Because changes in [Ca(2+)](i) affect chemotaxis, secretion, and gene expression, pharmacologic modulation of this pathway may alter inflammatory and degenerative processes in the CNS.

L3 ANSWER 23 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006266857 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16696176
TITLE: Cytotoxicity and transcriptional activation of stress genes in human liver carcinoma (HepG2) cells exposed to iprodione.
AUTHOR: Washington Teresa; Tchounwou Paul B
CORPORATE SOURCE: Molecular Toxicology Research Laboratory, NIH-Center for Environmental Health, School of Science and Technology, Jackson State University, Jackson, Mississippi, USA.
CONTRACT NUMBER: 1G12RR13459 (NCRR)
SOURCE: International journal of environmental research and public health, (2004 Mar) Vol. 1, No. 1, pp. 12-20. Journal code: 101238455. ISSN: 1661-7827.
PUB. COUNTRY: Switzerland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL) (RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200605
ENTRY DATE: Entered STN: 16 May 2006
Last Updated on STN: 1 Jun 2006
Entered Medline: 31 May 2006

AB Iprodione (C13H13Cl2N3O3) is a broad spectrum dicarboximide fungicide used on a wide variety of crop diseases. It is used on vegetables, ornamentals, pome and stone fruit, root crops, cotton and sunflowers, to control a variety of fungal pests. Iprodione inhibits the germination of spores and the growth of the fungal mycelium. Experimental studies with mice have indicated that exposure to iprodione at dose levels 5 to 15 folds greater than the LOAEL for liver injury, induces microsomal enzyme activities, hepatocyte proliferation, hepatomegaly, centrilobular hypertrophy, diffuse hypertrophy, and an increase in lauric acid hydroxylation. Currently, there is no toxicological data available on human health effects associated with exposure to iprodione. In this research, we performed the MTT Assay for cell viability to assess the cytotoxicity of iprodione, and the CAT-Tox (L) assay to measure the induction of stress genes in thirteen recombinant cell lines generated from human liver carcinoma cells (HepG2). The cytotoxicity data indicated a strong concentration-response relationship with regard to iprodione toxicity. The percentages of cell viability were 100 +/- 0%, 128.0 +/- 41.4%, 97.5 +/- 37.7%, 70.1 +/- 35.4%, 33.5 +/- 16.1%, and 5.1 +/- 3.7% in 0, 31.3, 62.5, 125, 250, and 500 microg/mL, respectively. The LC50 was 208.3 +/- 83.3 microg/mL. Data obtained from the CAT-Tox (L) assay showed that iprodione is able to induce a significant number of stress genes in HepG2 cells. At 250 ug/mL exposure, the induction levels were 1.2 +/- 0.4, 50.1 +/- 17.8, 3.9 +/- 1.2, 16.8 +/- 7.2, 10.7 +/- 0.7, 1.8 +/- 0, 26.3 +/- 10.0, 7.2 +/- 2.4, 1.8 +/- 0.0, 6.8 +/- 1.3, 6.7 +/- 0.5, and 4.3 +/- 1.8 for CYP1A1, GSTYa, XRE, HMTIIA, c-fos, NF-kBRE, HSP70, CRE, RARE, GADD153, GADD45, and GRP78, respectively. These results indicate that the metabolism of iprodione involves Phase II biotransformation in the liver (XRE, GSTYa), and that this chemical has the potential to cause cell proliferation and/or inflammatory reactions (c-fos, NF-kB), proteotoxic effects (HSP70, GRP78), metabolic disruption (CRE), and DNA damage (GADD45, GADD153).

L3 ANSWER 24 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2006010345 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16225456
TITLE: Extracellular NAD+ regulates intracellular calcium levels and induces activation of human granulocytes.
AUTHOR: Bruzzone Santina; Moreschi Iliana; Guida Lucrezia; Usai Cesare; Zocchi Elena; De Flora Antonio
CORPORATE SOURCE: Department of Experimental Medicine, Section of Biochemistry, and Center of Excellence for Biomedical Research, University of Genova, Viale Benedetto XV/1, 16132

Genova, Italy.
SOURCE: The Biochemical journal, (2006 Feb 1) Vol. 393, No. Pt 3, pp. 697-704.
Journal code: 2984726R. E-ISSN: 1470-8728.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200603
ENTRY DATE: Entered STN: 7 Jan 2006
Last Updated on STN: 25 Mar 2006
Entered Medline: 24 Mar 2006

AB Beta-NAD+e (extracellular beta-NAD+), present at nanomolar levels in human plasma, has been implicated in the regulation of [Ca2+]i (the intracellular calcium concentration) in various cell types, including blood cells, by means of different mechanisms. Here, we demonstrate that micromolar NAD+e (both the alpha and the beta extracellular NAD+ forms) induces a sustained [Ca2+]i increase in human granulocytes by triggering the following cascade of causally related events: (i) activation of adenylate cyclase and overproduction of cAMP; (ii) activation of protein kinase A; (iii) stimulation of ADP-ribosyl cyclase activity and consequent overproduction of cADP-ribose, a universal Ca2+ mobilizer; and (iv) influx of extracellular Ca2+. The NAD+e-triggered [Ca2+]i elevation translates into granulocyte activation, i.e. superoxide and nitric oxide generation, and enhanced chemotaxis in response to 0.1-10 microM NAD+e. Thus extracellular beta-NAD+e behaves as a novel pro-inflammatory cytokine, stimulating human granulocytes and potentially recruiting them at sites of inflammation.

L3 ANSWER 25 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2005523230 MEDLINE
DOCUMENT NUMBER: PubMed ID: 16168959
TITLE: Non-specific effects of 4-chloro-m-cresol may cause calcium flux and respiratory burst in human neutrophils.
AUTHOR: Hauser Carl J; Kannan Kolenkode B; Deitch Edwin A; Itagaki Kiyoshi
CORPORATE SOURCE: The Department of Surgery, Division of Trauma, UMDNJ-New Jersey Medical School, Newark, 07103, USA.
SOURCE: Biochemical and biophysical research communications, (2005 Nov 4) Vol. 336, No. 4, pp. 1087-95.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200512
ENTRY DATE: Entered STN: 4 Oct 2005
Last Updated on STN: 18 Dec 2005
Entered Medline: 12 Dec 2005

AB We examined the effects of 4-chloro-m-cresol (4-CmC, a potent and specific activator of ryanodine receptors) on Ca(2+)-release/influx and respiratory burst in freshly isolated human PMN as well as HL60 cells. 4-CmC induces Ca(2+) store-depletion in a dose-dependent manner at concentrations between 400muM and 3mM, however no dose-dependent effect on Ca(2+)-influx was found. 4-CmC depleted Ca(2+) stores that were shared with the GPC agonists such as fMLP and PAF, and therefore 4-CmC presumably depletes Ca(2+) from ER. Since the authentic ligand for RyR is cyclic ADP-ribose (cADPR), we assessed the functional relevance of RyR in PMN by studying the presence and function of membrane-bound ADP-ribosyl cyclase (CD38) in PMN. First, expression of CD38 was confirmed by RT-PCR using cDNA from HL60 cells. Second, PMN from trauma patients showed significantly enhanced CD38 expression than those from healthy volunteers. In addition, although no chemotaxis effect was detected by 4-CmC, it stimulated

respiratory burst in PMN in a dose-dependent manner. Our findings suggest that RyRs exist in human PMN and that RyR pathway may play an active role in inflammatory PMN calcium signaling. 8-Br-cADPR and cyclic 3-deaza-ADP did not have inhibitory effects either on 4-CmC-induced Ca(2+) store-depletion or on respiratory burst, on the other hand, PLC inhibitor, U73122, completely attenuated both 4-CmC-induced Ca(2+) store-depletion and respiratory burst. Although it has been used as a specific activator of RyR, 4-CmC has non-specific effects which cause Ca(2+) store-depletion and respiratory burst at least in human PMN.

L3 ANSWER 26 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2004383527 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15266023
TITLE: Tumor necrosis factor-alpha differentially regulates the expression of proinflammatory genes in human airway smooth muscle cells by activation of interferon-beta-dependent CD38 pathway.
AUTHOR: Tliba Omar; Panettieri Reynold A Jr; Tliba Samira; Walseth Timothy F; Amrani Yassine
CORPORATE SOURCE: Pulmonary, Allergy, and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania 19104-6160, USA.
CONTRACT NUMBER: 2R01-HL55301 (NHLBI)
DA11806 (NIDA)
HL67663 (NHLBI)
SOURCE: Molecular pharmacology, (2004 Aug) Vol. 66, No. 2, pp. 322-9.
Journal code: 0035623. ISSN: 0026-895X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200408
ENTRY DATE: Entered STN: 4 Aug 2004
Last Updated on STN: 31 Aug 2004
Entered Medline: 30 Aug 2004

AB Recent evidence suggests that CD38, an ectoenzyme that converts NAD(+) to cyclic ADP-ribose (cADPr), may play a role in cytokine-induced airway smooth muscle (ASM) cell hyper-responsiveness, a key feature associated with chronic asthma. In the present study, we investigated the major signaling pathways by which tumor necrosis factor-alpha (TNFalpha) induces CD38 expression and its role in regulating gene expression in human ASM cells. Using flow cytometry analyses, TNFalpha enhanced CD38 expression in a manner that was time-(0-24 h), concentration-(0.1-40 ng/ml), and protein synthesis-(cycloheximide blockade) dependent. A selective agonistic antibody against tumor necrosis factor receptor (TNFR) 1 also augmented CD38 expression, whereas anti-TNFR2 antagonistic antibody did not prevent the TNFalpha response. Inhibition of the Janus activated kinase/signal transducer and activator of transcription pathways using the soluble inhibitor 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz-[h]imidaz[4,5-f]isoquinolin-7-one (DBI) or with neutralizing antibody against interferon beta (IFNbeta) completely abrogated TNFalpha-induced CD38 expression at both protein and mRNA levels. Combining TNFalpha (0.1 and 1 ng/ml) and IFNbeta (100 IU/ml) at concentrations alone that had little effect on CD38 expression induced a robust synergistic induction of CD38 mRNA and protein levels. 8-Bromo-cADPr, a cADPr antagonist, significantly augmented TNFalpha-induced interleukin-6 secretion, whereas regulated on activation normal T cell expressed and secreted secretion was suppressed. 8-Bromo-cADPr, however, did not affect TNFalpha-induced cell surface expression of intercellular adhesion molecule-1. Our study is the first to demonstrate that IFNbeta-dependent activation of CD38 pathway is a novel component by which TNFalpha differentially regulates the

expression of inflammatory genes in ASM cells.

L3 ANSWER 27 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2004047399 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14734775
TITLE: Chemotaxis and calcium responses of phagocytes to formyl peptide receptor ligands is differentially regulated by cyclic ADP ribose.
AUTHOR: Partida-Sanchez Santiago; Iribarren Pablo; Moreno-Garcia Miguel E; Gao Ji-Liang; Murphy Philip M; Oppenheimer Norman; Wang Ji Ming; Lund Frances E
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY 12983, USA.
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (2004 Feb 1) Vol. 172, No. 3, pp. 1896-906.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200405
ENTRY DATE: Entered STN: 30 Jan 2004
Last Updated on STN: 10 May 2004
Entered Medline: 7 May 2004

AB Cyclic ADP ribose (cADPR) is a calcium-mobilizing metabolite that regulates intracellular calcium release and extracellular calcium influx. Although the role of cADPR in modulating calcium mobilization has been extensively examined, its potential role in regulating immunologic responses is less well understood. We previously reported that cADPR, produced by the ADP-ribosyl cyclase, CD38, controls calcium influx and chemotaxis of murine neutrophils responding to fMLF, a peptide agonist for two chemoattractant receptor subtypes, formyl peptide receptor and formyl peptide receptor-like 1. In this study, we examine whether cADPR is required for chemotaxis of human monocytes and neutrophils to a diverse array of chemoattractants. We found that a cADPR antagonist and a CD38 substrate analogue inhibited the chemotaxis of human phagocytic cells to a number of formyl peptide receptor-like 1-specific ligands but had no effect on the chemotactic response of these cells to ligands selective for formyl peptide receptor. In addition, we show that the cADPR antagonist blocks the chemotaxis of human monocytes to CXCR4, CCR1, and CCR5 ligands. In all cases, we found that cADPR modulates intracellular free calcium levels in cells activated by chemokines that induce extracellular calcium influx in the apparent absence of significant intracellular calcium release. Thus, cADPR regulates calcium signaling of a discrete subset of chemoattractant receptors expressed by human leukocytes. Since many of the chemoattractant receptors regulated by cADPR bind to ligands that are associated with clinical pathology, cADPR and CD38 represent novel drug targets with potential application in chronic inflammatory and neurodegenerative disease.

L3 ANSWER 28 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001640125 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11689885
TITLE: Cyclic ADP-ribose production by CD38 regulates intracellular calcium release, extracellular calcium influx and chemotaxis in neutrophils and is required for bacterial clearance in vivo.
AUTHOR: Partida-Sanchez S; Cockayne D A; Monard S; Jacobson E L; Oppenheimer N; Garvy B; Kusser K; Goodrich S; Howard M; Harmsen A; Randall T D; Lund F E
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, New York, USA.
SOURCE: Nature medicine, (2001 Nov) Vol. 7, No. 11, pp. 1209-16.
Journal code: 9502015. ISSN: 1078-8956.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 7 Nov 2001
Last Updated on STN: 18 Dec 2002
Entered Medline: 7 Dec 2001

AB Cyclic ADP-ribose is believed to be an important calcium-mobilizing second messenger in invertebrate, mammalian and plant cells. CD38, the best-characterized mammalian ADP-ribosyl cyclase, is postulated to be an important source of cyclic ADP-ribose in vivo. Using CD38-deficient mice, we demonstrate that the loss of CD38 renders mice susceptible to bacterial infections due to an inability of CD38-deficient neutrophils to directionally migrate to the site of infection. Furthermore, we show that cyclic ADP-ribose can directly induce intracellular Ca++ release in neutrophils and is required for sustained extracellular Ca++ influx in neutrophils that have been stimulated by the bacterial chemoattractant, formyl-methionyl-leucyl-phenylalanine (fMLP). Finally, we demonstrate that neutrophil chemotaxis to fMLP is dependent on Ca++ mobilization mediated by cyclic ADP-ribose. Thus, CD38 controls neutrophil chemotaxis to bacterial chemoattractants through its production of cyclic ADP-ribose, and acts as a critical regulator of inflammation and innate immune responses.

L3 ANSWER 29 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2001453688 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11483668
TITLE: Evidence of a role for cyclic ADP-ribose in calcium signalling and neurotransmitter release in cultured astrocytes.
AUTHOR: Verderio C; Bruzzone S; Zocchi E; Fedele E; Schenk U; De Flora A; Matteoli M
CORPORATE SOURCE: CNR Cellular and Molecular Pharmacology and B. Ceccarelli Centers, Department of Medical Pharmacology, University of Milan, Milan, Italy.
SOURCE: Journal of neurochemistry, (2001 Aug) Vol. 78, No. 3, pp. 646-57.
Journal code: 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 14 Aug 2001
Last Updated on STN: 18 Dec 2002
Entered Medline: 30 Aug 2001

AB Astrocytes possess different, efficient ways to generate complex changes in intracellular calcium concentrations, which allow them to communicate with each other and to interact with adjacent neuronal cells. Here we show that cultured hippocampal astrocytes coexpress the ectoenzyme CD38, directly involved in the metabolism of the calcium mobilizer cyclic ADP-ribose, and the NAD+ transporter connexin 43. We also demonstrate that hippocampal astrocytes can release NAD+ and respond to extracellular NAD+ or cyclic ADP-ribose with intracellular calcium increases, suggesting the existence of an autocrine cyclic ADP-ribose-mediated signalling. Cyclic ADP-ribose-induced calcium changes are in turn responsible for an increased glutamate and GABA release, this effect being completely inhibited by the cyclic ADP-ribose specific antagonist 8-NH2-cADPR. Furthermore, addition of NAD+ to astrocyte-neuron co-cultures results in a delayed intracellular calcium transient in neuronal cells, which is strongly but not completely inhibited by glutamate receptor blockers. These data indicate that an astrocyte-to-neuron calcium signalling can be

triggered by the CD38/cADPR system, which, through the activation of intracellular calcium responses in astrocytes, is in turn responsible for the increased release of neuromodulators from glial cells.

L3 ANSWER 30 OF 30 MEDLINE on STN
ACCESSION NUMBER: 97332695 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9188506
TITLE: Role of cyclic ADP-ribose in ATP-activated potassium currents in alveolar macrophages.
AUTHOR: Ebihara S; Sasaki T; Hida W; Kikuchi Y; Oshiro T; Shimura S; Takasawa S; Okamoto H; Nishiyama A; Akaike N; Shirato K
CORPORATE SOURCE: First Department of Internal Medicine, Tohoku University School of Medicine, Sendai 980-77, Japan.
SOURCE: The Journal of biological chemistry, (1997 Jun 20) Vol. 272, No. 25, pp. 16023-9.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 5 Aug 1997
Last Updated on STN: 10 Dec 2002
Entered Medline: 21 Jul 1997

AB There is growing evidence that extracellular ATP causes a dramatic change in the membrane conductance of a variety of inflammatory cells. In the present study, using the nystatin perforated patch recording configuration, we found that ATP (0.3-30 microM) induced a transient outward current in a concentration-dependent manner and that the reversal potential of the ATP-induced outward current was close to the K+ equilibrium potential, indicating that the membrane behaves like a K+ electrode in the presence of ATP. The first application of ATP to alveolar macrophages perfused with Ca2+-free external solution could induce the outward current, but the response to ATP was diminished with successive applications. Intracellular perfusion with a Ca2+ chelator, 1,2-bis(2-aminophenoxy)ethane-N,N,N', N'-tetraacetic acid, also diminished the response. When cyclic ADP-ribose (cADPR) was applied to the macrophage cytoplasm, a transient outward current was elicited. Thereafter, the successive outward current was inhibited, suggesting the involvement of cADPR in the response. Intracellular perfusion with inositol 1,4, 5-trisphosphate also induced a transient outward current, but the successive current was not inhibited. The ATP-induced outward current was abolished when 8-amino-cADPR (as a blocker of cADPR, 10(-6)-10(-5) M) was introduced into the cytoplasm. Homogenates of alveolar macrophages showed both ADP-ribosyl cyclase and cADPR hydrolase activities, and CD38 (ADP-ribosyl cyclase/cADPR hydrolase) expression was confirmed by reverse transcriptase-polymerase chain reaction and Western blot analyses. These results indicate that ATP activates K+ currents by releasing Ca2+ from cADPR-sensitive internal Ca2+ stores.

L3 ANSWER 10 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:93934 CAPLUS
DOCUMENT NUMBER: 140:162333
TITLE: Chemotaxis and calcium responses of phagocytes to formyl peptide receptor ligands is differentially regulated by cyclic ADP ribose
AUTHOR(S): Partida-Sanchez, Santiago; Iribarren, Pablo; Moreno-Garcia, Miguel E.; Gao, Ji-Liang; Murphy, Philip M.; Oppenheimer, Norman; Wang, Ji Ming; Lund, Frances E.
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY, 12983, USA
SOURCE: Journal of Immunology (2004), 172(3), 1896-1906
CODEN: JOIMA3; ISSN: 0022-1767
PUBLISHER: American Association of Immunologists
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic ADP ribose (cADPR) is a calcium-mobilizing metabolite that regulates intracellular calcium release and extracellular calcium influx. Although the role of cADPR in modulating calcium mobilization has been extensively examined, its potential role in regulating immunol. responses is less well understood. The authors previously reported that cADPR, produced by the ADP-ribosyl cyclase, CD38, controls calcium influx and chemotaxis of murine neutrophils responding to fMLF, a peptide agonist for two chemoattractant receptor subtypes, formyl peptide receptor and formyl peptide receptor-like 1. Here, they examine whether cADPR is required for chemotaxis of human monocytes and neutrophils to a diverse array of chemoattractants. They found that a cADPR antagonist and a CD38 substrate analog inhibited the chemotaxis of human phagocytic cells to a number of formyl peptide receptor-like 1-specific ligands but had no effect on the chemotactic response of these cells to ligands selective for formyl peptide receptor. In addition, the authors show that the cADPR antagonist blocks the chemotaxis of human monocytes to CXCR4, CCR1, and CCR5 ligands. In all cases, the authors found that cADPR modulates intracellular free calcium levels in cells activated by chemokines that induce extracellular calcium influx in the apparent absence of intracellular calcium release. Thus, cADPR regulates calcium signaling of a discrete subset of chemoattractant receptors expressed by human leukocytes. Since many of the chemoattractant receptors regulated by cADPR bind to ligands that are associated with clin. pathol., cADPR and CD38 represent novel drug targets with potential application in chronic inflammatory and neurodegenerative disease.
REFERENCE COUNT: 64 THERE ARE 64 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 11 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:744512 CAPLUS
DOCUMENT NUMBER: 140:403778
TITLE: Calcium regulation in smooth muscle through the CD38/cyclic ADP-ribose pathway
AUTHOR(S): White, Thomas A.; Deshpande, Deepak A.; Dogan, Soner; Panettieri, Reynold A.; Walseth, Timothy F.; Kannan, Mathur S.
CORPORATE SOURCE: Department of Veterinary PathoBiology, College of Veterinary Medicine, University of Minnesota, St. Paul, MN, USA
SOURCE: Cyclic ADP-Ribose and NAADP (2002), 427-449.
Editor(s): Lee, Hon Cheung. Kluwer Academic Publishers: Norwell, Mass.
CODEN: 69ENI2; ISBN: 1-4020-7281-3
DOCUMENT TYPE: Conference; General Review
LANGUAGE: English
AB A review on the role of the CD38/cyclic ADP-ribose (cADPR) pathway of Ca2+ regulation in airway, vascular, uterine, and intestinal smooth muscles.

Evidence for regulation of CD38 expression in smooth muscles by hormones and inflammatory mediators is provided. The mechanisms by which cADPR causes Ca2+ release from the sarcoplasmic reticulum in different smooth muscles are also discussed.

REFERENCE COUNT: 100 THERE ARE 100 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 12 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:212944 CAPLUS
DOCUMENT NUMBER: 138:367397
TITLE: CD38-cyclic ADP-ribose-mediated Ca2+ signaling contributes to airway smooth muscle hyperresponsiveness
AUTHOR(S): Deshpande, Deepak A.; Walseth, Timothy F.; Panettieri, Reynold A.; Kannan, Mathur S.
CORPORATE SOURCE: Departments of Veterinary PathoBiology and Pharmacology, University of Minnesota, St. Paul, MN, 55108, USA
SOURCE: FASEB Journal (2003), 17(3), 452-454, 10.1096/fj.02-0450fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We previously demonstrated that cyclic ADP-ribose (cADPR) elicits Ca2+ release in airway smooth muscle (ASM) cells through ryanodine receptor channels. CD38 is a cell surface protein that catalyzes the synthesis and degradation of cADPR. In inflammatory diseases such as asthma, augmented Ca2+ responses and Ca2+ sensitivity contribute to increased ASM contractility in response to agonists. In this study, we investigated the regulation of CD38 expression and the role of cADPR-mediated Ca2+ release in airway inflammation. Human ASM cells in culture between the second and fifth passages were exposed to tumor necrosis factor α (TNF-α), interleukin 1β, or interferon γ, or bovine serum albumin (controls). CD38 expression was measured by reverse transcriptase-polymerase chain reaction (RT-PCR), real-time PCR, and Western blot anal., and ADP-ribosyl cyclase activity was assayed with nicotinamide guanine dinucleotide as the substrate. Ca2+ responses to acetylcholine, bradykinin, and thrombin were measured in fura-2AM-loaded cells by fluorescence microscopy. Cytokines caused significant augmentation of CD38 expression, ADP-ribosyl cyclase activity, and Ca2+ responses to the agonists, compared with the control. TNF-α effects were greater than those of the other two cytokines. The cADPR antagonist 8-bromo-cADPR attenuated the Ca2+ responses to the agonists in control and cytokine-treated cells, with the magnitude of inhibition correlating with the level of CD38. This study provides the first demonstration of a role for CD38-cADPR signaling in a model of inflammatory airway disease.

REFERENCE COUNT: 65 THERE ARE 65 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:946087 CAPLUS
DOCUMENT NUMBER: 138:11408
TITLE: ADP ribosyl cyclase inhibitors for treating autoimmune and inflammatory disorders
INVENTOR(S): Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Schweitzer, Katrin
PATENT ASSIGNEE(S): University of Bath, UK
SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002098397	A2	20021212	WO 2002-GB2695	20020606
WO 2002098397	A3	20030313		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002310623	A1	20021216	AU 2002-310623	20020606
GB 2392095	A	20040225	GB 2003-28165	20020606
EP 1395267	A2	20040310	EP 2002-735614	20020606
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2004214789	A1	20041028	US 2003-730589	20031208
PRIORITY APPLN. INFO.:			GB 2001-13923 A	20010607
			WO 2002-GB2695 W	20020606

OTHER SOURCE(S): MARPAT 138:11408

AB The use of a compound of formula A-L-B wherein A and B are independently selected from a cyclic ring, wherein each of which cyclic rings A and B may be optionally substituted at at least one ring position; and L is a suitable linker; or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inhibiting ADP-ribosyl cyclase.

L3 ANSWER 14 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:696553 CAPLUS
DOCUMENT NUMBER: 137:231357
TITLE: Schistosoma mansoni-derived chemotactic SM38 protein for screening drugs capable of modulating CD38-modulated chemotaxis and treating related diseases
INVENTOR(S): Lund, Frances E.; Randall, Troy D.; Partida-Sanchez, Santiago
PATENT ASSIGNEE(S): Trudeau Institute, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 41 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002127646	A1	20020912	US 2001-982616	20011017
US 6955884	B2	20051018		
CA 2424643	A1	20020425	CA 2001-2424643	20011017
WO 2002032288	A2	20020425	WO 2001-US32383	20011017
WO 2002032288	A3	20020711		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR,				

IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

EP 1326998	A2	20030716	EP 2001-981689	20011017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004518414	T	20040624	JP 2002-535531	20011017
US 2006019308	A1	20060126	US 2005-58924	20050215
US 2007042436	A1	20070222	US 2005-115964	20050426
PRIORITY APPLN. INFO.:			US 2000-241065P	P 20001017
			US 2001-982616	A2 20011017
			WO 2001-US32383	W 20011017
			US 2005-58924	A2 20050215

AB The present invention relates to methods for modulating the migratory activity of cells expressing CD38 for the treatment of disorders including, but not limited to, inflammation, ischemia, asthma, autoimmune disease, diabetes, arthritis, allergies, infection with pathogenic organisms and transplant rejection. Such cells include, for example, neutrophils, lymphocytes, eosinophils, macrophages and dendritic cells. The invention further relates to drug screening assays designed to identify compds. that modulate the ADP-ribosyl cyclase activity of CD38 and the use of such compds. in the treatment of disorders involving CD38 modulated cell migration. The invention is based on the discovery that CD38 ADP-ribosyl cyclase activity is required for chemotaxis. Furthermore, the invention relates to methods for identifying compds. that modulate the enzyme activity of the S. mansoni CD38 homolog and using those compds. in the treatment of pathol. disorders caused by helminth infection. This is based on the discovery that helminths such as S. mansoni express CD38 homologues.

L3 ANSWER 15 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER:	2002:122798 CAPLUS
DOCUMENT NUMBER:	136:177974
TITLE:	Nicotinic acid adenine dinucleotide phosphate (NAADP) analogs for modulating T-cell activity
INVENTOR(S):	Potter, Barry V. L.; Guse, Andreas H.; Mayr, Georg W.; Berg, Ingeborg
PATENT ASSIGNEE(S):	University of Bath, UK
SOURCE:	PCT Int. Appl., 83 pp. CODEN: PIXXD2
DOCUMENT TYPE:	Patent
LANGUAGE:	English
FAMILY ACC. NUM. COUNT:	1
PATENT INFORMATION:	

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002011736	A1	20020214	WO 2001-GB3440	20010731
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 200175732	A	20020218	AU 2001-75732	20010731
EP 1305035	A1	20030502	EP 2001-953243	20010731
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
US 2005119197	A1	20050602	US 2004-343667	20040927
PRIORITY APPLN. INFO.:			GB 2000-19234	A 20000804
			WO 2001-GB3440	W 20010731
OTHER SOURCE(S):	MARPAT 136:177974			

AB A method for modulating T cell activity by modulating the intracellular concentration and/or activity of NAADP+, compds. capable of modulating the effect of NAADP+ on T cell Ca+2 levels, and methods for identifying such compds., are described. Preparation of 8-bromo-nicotinic acid adenine dinucleotide phosphate is described.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 16 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2001:836694 CAPLUS
DOCUMENT NUMBER: 136:117332
TITLE: Cyclic ADP-ribose production by CD38 regulates intracellular calcium release, extracellular calcium influx and chemotaxis in neutrophils and is required for bacterial clearance in vivo
AUTHOR(S): Partida-Sanchez, Santiago; Cockayne, Debra A.; Monard, Simon; Jacobson, Elaine L.; Oppenheimer, Norman; Garvy, Beth; Kusser, Klm; Goodrich, Stephen; Howard, Maureen; Harmsen, Allen; Randall, Troy D.; Lund, Frances E.
CORPORATE SOURCE: Trudeau Institute, Saranac Lake, NY, USA
SOURCE: Nature Medicine (New York, NY, United States) (2001), 7(11), 1209-1216
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cyclic ADP-ribose is believed to be an important calcium-mobilizing second messenger in invertebrate, mammalian and plant cells. CD38, the best-characterized mammalian ADP-ribosyl cyclase, is postulated to be an important source of cyclic ADP-ribose in vivo. Using CD38-deficient mice, we demonstrate that the loss of CD38 renders mice susceptible to bacterial infections due to an inability of CD38-deficient neutrophils to directionally migrate to the site of infection. Furthermore, we show that cyclic ADP-ribose can directly induce intracellular Ca++ release in neutrophils and is required for sustained extracellular Ca++ influx in neutrophils that have been stimulated by the bacterial chemoattractant, formyl-methionyl-leucyl-phenylalanine (fMLP). Finally, we demonstrate that neutrophil chemotaxis to fMLP is dependent on Ca++ mobilization mediated by cyclic ADP-ribose. Thus, CD38 controls neutrophil chemotaxis to bacterial chemoattractants through its production of cyclic ADP-ribose, and acts as a critical regulator of inflammation and innate immune responses.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 17 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2000:569665 CAPLUS
DOCUMENT NUMBER: 133:249795
TITLE: Nitric oxide and salicylic acid signaling in plant defense
AUTHOR(S): Klessig, Daniel F.; Durner, Jorg; Noad, Robert; Navarre, Duroy A.; Wendehenne, David; Kumar, Dhirendra; Zhou, Jun Ma; Shah, Jyoti; Zhang, Shuqun; Kachroo, Pradeep; Trifa, Youssef; Pontier, Dominique; Lam, Eric; Silva, Herman
CORPORATE SOURCE: Waksman Institute and Department of Molecular Biology and Biochemistry, Rutgers, The State University of New Jersey, Piscataway, NJ, 08854-8020, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(16), 8849-8855
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences

DOCUMENT TYPE: Journal
LANGUAGE: English
AB Salicylic acid (SA) plays a critical signaling role in the activation of plant defense responses after pathogen attack. Several potential components of the SA signaling pathway were identified, including (i) the H2O2-scavenging enzymes catalase and ascorbate peroxidase, (ii) a high affinity SA-binding protein (SABP2), (iii) a SA-inducible protein kinase (SIPK), (iv) NPR1, an ankyrin repeat-containing protein that exhibits limited homol. to IκBα and is required for SA signaling, and (v) members of the TGA/OBF family of bZIP transcription factors. These bZIP factors phys. interact with NPR1 and bind the SA-responsive element in promoters of several defense genes, such as the pathogenesis-related 1 gene (PR-1). Nitric oxide (NO) is another signal that activates defense responses after pathogen attack. NO plays a critical role in the activation of innate immune and inflammatory responses in animals. Increases in NO synthase (NOS)-like activity occurred in resistant but not susceptible tobacco after infection with tobacco mosaic virus. Here we demonstrate that this increase in activity participates in PR-1 gene induction. Two signaling mols., cGMP and cyclic ADP ribose (cADPR), which function downstream of NO in animals, also appear to mediate plant defense gene activation (e.g., PR-1). Addnl., NO may activate PR-1 expression via an NO-dependent, cADPR-independent pathway. Several targets of NO in animals, including guanylate cyclase, aconitase, and mitogen-activated protein kinases (e.g., SIPK), are also modulated by NO in plants. Thus, at least portions of NO signaling pathways appear to be shared between plants and animals.
REFERENCE COUNT: 75 THERE ARE 75 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 18 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 1997:415458 CAPLUS
DOCUMENT NUMBER: 127:134649
TITLE: Role of cyclic ADP-ribose in ATP-activated potassium currents in alveolar macrophages
AUTHOR(S): Ebihara, Satoru; Sasaki, Tsukasa; Hida, Wataru; Kikuchi, Yoshihiro; Oshiro, Takako; Shimura, Sanae; Takasawa, Shin; Okamoto, Hiroshi; Nishiyama, Akinori; Akaike, Norio; Shirato, Kunio
CORPORATE SOURCE: First Department of Internal Medicine, the Department of Biochemistry, and the First Department of Physiology, Tohoku University School of Medicine, Sendai, 980-77, Japan
SOURCE: Journal of Biological Chemistry (1997), 272(25), 16023-16029
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB There is growing evidence that extracellular ATP causes a dramatic change in the membrane conductance of a variety of inflammatory cells. In the present study, using the nystatin perforated patch recording configuration, the authors found that ATP (0.3-30 μM) induced a transient outward current in a concentration-dependent manner and that the reversal potential of the ATP-induced outward current was close to the K+ equilibrium potential, indicating that the membrane behaves like a K+ electrode in the presence of ATP. The first application of ATP to alveolar macrophages perfused with Ca2+-free external solution could induce the outward current, but the response to ATP was diminished with successive applications. Intracellular perfusion with a Ca2+ chelator, BAPTA, also diminished the response. When cyclic ADP-ribose (cADPR) was applied to the macrophage cytoplasm, a transient outward current was elicited. Thereafter, the successive outward current was inhibited, suggesting the involvement of cADPR in the response. Intracellular perfusion with

inositol 1,4,5-trisphosphate also induced a transient outward current, but the successive current was not inhibited. The ATP-induced outward current was abolished when 8-amino-cADPR (as a blocker of cADPR, 10-6-10-5 M) was introduced into the cytoplasm. Homogenates of alveolar macrophages showed both ADP-ribosyl cyclase and cADPR hydrolase activities, and CD38 (ADP-ribosyl cyclase/cADPR hydrolase) expression was confirmed by reverse transcriptase-polymerase chain reaction and Western blot analyses. These results indicate that ATP activates K+ currents by releasing Ca2+ from cADPR-sensitive internal Ca2+ stores.

L3 ANSWER 19 OF 30 MEDLINE on STN
ACCESSION NUMBER: 2007203139 MEDLINE
DOCUMENT NUMBER: PubMed ID: 17389374
TITLE: Abscisic acid is an endogenous cytokine in human granulocytes with cyclic ADP-ribose as second messenger.
AUTHOR: Bruzzone Santina; Moreschi Iliana; Usai Cesare; Guida Lucrezia; Damonte Gianluca; Salis Annalisa; Scarfi Sonia; Millo Enrico; De Flora Antonio; Zocchi Elena
CORPORATE SOURCE: Department of Experimental Medicine, Section of Biochemistry, University of Genova, Viale Benedetto XV/1, 16132 Genoa, Italy.
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (2007 Apr 3) Vol. 104, No. 14, pp. 5759-64. Electronic Publication: 2007-03-26. Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200706
ENTRY DATE: Entered STN: 5 Apr 2007
Last Updated on STN: 30 Jun 2007
Entered Medline: 29 Jun 2007

AB Abscisic acid (ABA) is a phytohormone involved in fundamental physiological processes of higher plants, such as response to abiotic stress (temperature, light, drought), regulation of seed dormancy and germination, and control of stomatal closure. Here, we provide evidence that ABA stimulates several functional activities [phagocytosis, reactive oxygen species and nitric oxide (NO) production, and chemotaxis] of human granulocytes through a signaling pathway sequentially involving a pertussis toxin (PTX)-sensitive G protein/receptor complex, protein kinase A activation, ADP-ribosyl cyclase phosphorylation, and consequent cyclic-ADP-ribose overproduction, leading to an increase of the intracellular Ca(2+) concentration. The increase of free intracellular ABA and its release by activated human granulocytes indicate that ABA should be considered as a new pro-inflammatory cytokine in humans. This discovery is an intriguing example of conservation of a hormone and its signaling pathway from plants to humans and provides insight into the molecular mechanisms of granulocyte activation, possibly leading to the development of new antiinflammatory drugs.

L3 ANSWER 1 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:426335 CAPLUS
DOCUMENT NUMBER: 146:499091
TITLE: Abscisic acid is an endogenous cytokine in human granulocytes with cyclic ADP-ribose as second messenger
AUTHOR(S): Bruzzone, Santina; Moreschi, Iliana; Usai, Cesare; Guida, Lucrezia; Damonte, Gianluca; Salis, Annalisa; Scarfi, Sonia; Millo, Enrico; De Flora, Antonio; Zocchi, Elena
CORPORATE SOURCE: Department of Experimental Medicine, Section of Biochemistry, and Center of Excellence for Biomedical Research, University of Genova, Genoa, 16132, Italy
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2007), 104(14), 5759-5764
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Abscisic acid (ABA) is a phytohormone involved in fundamental physiol. processes of higher plants, such as response to abiotic stress (temperature, light, drought), regulation of seed dormancy and germination, and control of stomatal closure. Here, we provide evidence that ABA stimulates several functional activities [phagocytosis, reactive oxygen species and nitric oxide (NO) production, and chemotaxis] of human granulocytes through a signaling pathway sequentially involving a pertussis toxin (PTX)-sensitive G protein/receptor complex, protein kinase A activation, ADP-ribosyl cyclase phosphorylation, and consequent cyclic-ADP-ribose overprodn., leading to an increase of the intracellular Ca2+ concentration The increase of free intracellular ABA and its release by activated human granulocytes indicate that ABA should be considered as a new pro-inflammatory cytokine in humans. This discovery is an intriguing example of conservation of a hormone and its signaling pathway from plants to humans and provides insight into the mol. mechanisms of granulocyte activation, possibly leading to the development of new antiinflammatory drugs.
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2007:203162 CAPLUS
DOCUMENT NUMBER: 146:272533
TITLE: Identifying compounds modulating CD38 enzyme activity to regulate cell chemotaxis
INVENTOR(S): Lund, Frances E.; Randall, Troy D.; Partida-Sanchez, Santiago
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 70pp., Cont.-in-part of U.S. Ser. No. 58,924.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2007042436	A1	20070222	US 2005-115964	20050426
CA 2424643	A1	20020425	CA 2001-2424643	20011017
US 2002127646	A1	20020912	US 2001-982616	20011017
US 6955884	B2	20051018		
EP 1326998	A2	20030716	EP 2001-981689	20011017
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

JP 2004518414 T 20040624 JP 2002-535531 20011017
US 2006019308 A1 20060126 US 2005-58924 20050215
WO 2006088951 A2 20060824 WO 2006-US5314 20060214
WO 2006088951 A3 20070315

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2000-241065P P 20001017
US 2001-982616 A2 20011017
US 2005-58924 A2 20050215
WO 2001-US32383 W 20011017
US 2005-115964 A 20050426

AB The invention is based on the discovery that although CD38 ADP-ribosyl cyclase activity is not essential for the initial activation of granulocytes, it is critically important in regulating neutrophil chemotaxis. The present invention relates to methods for modulating the migratory activity of cells expressing CD38 for the treatment of disorders including, but not limited to, inflammation, ischemia, asthma, autoimmune disease, diabetes, arthritis, allergies, infection with pathogenic organisms, such as parasites, and transplant rejection. Such cells include, for example, neutrophils, lymphocytes, eosinophils, macrophages and dendritic cells. The invention further relates to drug screening assays designed to identify compds. that modulate the ADP-ribosyl cyclase activity of CD38 and the use of such. compds. in the treatment of disorders involving CD38 modulated cell migration. Addnl., the invention relates to the isolation and characterization of a CD38 homolog (SM38) from the parasitic flatworm, Schistosoma mansoni.

L3 ANSWER 3 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1152476 CAPLUS
DOCUMENT NUMBER: 146:25590
TITLE: Cyclic ADP-ribose is a second messenger in the lipopolysaccharide-stimulated activation of murine N9 microglial cell line
AUTHOR(S): Franco, Luisa; Bodrato, Nicoletta; Moreschi, Iliana; Usai, Cesare; Bruzzone, Santina; Scarfi, Sonia; Zocchi, Elena; De Flora, Antonio
CORPORATE SOURCE: Department of Experimental Medicine, Section of Biochemistry, University of Genova, Genoa, Italy
SOURCE: Journal of Neurochemistry (2006), 99(1), 165-176
CODEN: JONRA9; ISSN: 0022-3042
PUBLISHER: Blackwell Publishing Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Lipopolysaccharide, the main component of the cell wall of Gram-neg. bacteria, is known to activate microglial cells following its interaction with the CD14/Toll-like receptor complex (TLR-4). The activation pathway triggered by lipopolysaccharide in microglia involves enhanced basal levels of intracellular calcium ([Ca2+]i) and terminates with increased generation of cytokines/chemokines and nitric oxide. Here we demonstrate that in lipopolysaccharide-stimulated murine N9 microglial cells, cyclic ADP-ribose, a universal and potent Ca2+ mobilizer generated from NAD+ by ADP-ribosyl cyclases (ADPRC), behaves as a second messenger in the cell activation pathway. Lipopolysaccharide induced phosphorylation, mediated by multiple protein kinases, of the mammalian ADPRC CD38, which resulted

in significantly enhanced ADPRC activity and in a 1.7-fold increase in the concentration of intracellular cyclic ADP-ribose. This event was paralleled by doubling of the basal [Ca2+]i levels, which was largely prevented by the cyclic ADP-ribose antagonists 8-Br-cyclic ADP-ribose and ryanodine (by 75% and 88%, resp.). Both antagonists inhibited, although incompletely, functional events downstream of the lipopolysaccharide-induced microglia-activating pathway, i.e. expression of inducible nitric oxide synthase, over-production and release of nitric oxide and of tumor necrosis factor α. The identification of cyclic ADP-ribose as a key signal metabolite in the complex cascade of events triggered by lipopolysaccharide and eventually leading to enhanced generation of pro-inflammatory mols. may suggest a new therapeutic target for treatment of neurodegenerative diseases related to microglia activation.

REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 4 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1006557 CAPLUS
DOCUMENT NUMBER: 145:354705
TITLE: Human anti-human CD38 antibodies and conjugates for treatment of rheumatoid arthritis and multiple myeloma
INVENTOR(S): De Weers, Michel; Graus, Yvo; Oprins, Judith; Parren, Paul Parren; Van de Winkel, Jan; Van Vugt, Martine
PATENT ASSIGNEE(S): Genmab A/S, Den.
SOURCE: PCT Int. Appl., 296pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006099875	A1	20060928	WO 2006-DK166	20060323
WO 2006099875	A8	20070503		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA

PRIORITY APPLN. INFO.:		
DK 2005-429	A	20050323
US 2005-667579P	P	20050401
US 2005-696163P	P	20050701
US 2005-728561P	P	20051020

AB Isolated human monoclonal antibodies which bind to human CD38, and related antibody-based compns. and mols., are disclosed. Also disclosed are pharmaceutical compns. comprising the human antibodies, and therapeutic and diagnostic methods for using the human antibodies.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 5 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:844879 CAPLUS
DOCUMENT NUMBER: 145:270024
TITLE: Modulation of CD38-dependent chemotaxis
INVENTOR(S): Lund, Frances E.; Randall, Troy D.; Partida-Sandchez, Santiago

PATENT ASSIGNEE(S): Trudeau Institute, USA
SOURCE: PCT Int. Appl., 167pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006088951	A2	20060824	WO 2006-US5314	20060214
WO 2006088951	A3	20070315		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006019308	A1	20060126	US 2005-58924	20050215
US 2007042436	A1	20070222	US 2005-115964	20050426
PRIORITY APPLN. INFO.:			US 2005-58924 A	20050215
			US 2005-115964 A	20050426
			US 2000-241065P P	20001017
			US 2001-982616 A2	20011017

AB The authors disclose methods for modulating the migratory activity of cells expressing CD38 for the treatment of disorders including, but not limited to, inflammation, ischemia, asthma, autoimmune disease, diabetes, arthritis, allergies, infection with pathogenic organisms, such as parasites, and transplant rejection. Such cells include, for example, neutrophils, lymphocytes, eosinophils, macrophages and dendritic cells. In one embodiment, the authors disclose drug screening assays designed to identify compds. that modulate the ADP-ribosyl cyclase activity of CD38 and the use of such, compds. in the treatment of disorders involving CD38 modulated cell migration. Addnl., the invention relates to the isolation and characterization of a CD38 homolog from the parasitic flatworm, Schistosoma mansoni.

L3 ANSWER 6 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:637951 CAPLUS
DOCUMENT NUMBER: 145:122704
TITLE: CCL5 evokes calcium signals in microglia through a kinase-, phosphoinositide-, and nucleotide-dependent mechanism
AUTHOR(S): Shideman, C. R.; Hu, S.; Peterson, P. K.; Thayer, S. A.
CORPORATE SOURCE: Department of Pharmacology, University of Minnesota, Minneapolis, MN, USA
SOURCE: Journal of Neuroscience Research (2006), 83(8), 1471-1484
CODEN: JNREDK; ISSN: 0360-4012
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Microglia, the resident macrophages of the CNS, are responsible for the innate immune response in the brain and participate in the pathogenesis of certain neurodegenerative disorders. Chemokines initiate activation and migration of microglia. The β-chemokine CCL5 induces an elevation in intracellular calcium concentration ([Ca2+]i) in human microglia. Here, we

examined the signal transduction pathway linking activation of chemokine receptor CCR5 to an elevation in [Ca2+]i in cultured microglia by using pharmacol. approaches in combination with Fura-2-based digital imaging. The CCL5-induced response required Janus kinase (Jak) activity and the stimulation of an inhibitory G protein. Multiple downstream signaling pathways were involved, including phosphatidylinositol 3-kinase (PI3K), Bruton's tyrosine kinase (Btk), and phospholipase C (PLC)-mediated release of Ca2+ from inositol 1,4,5-trisphosphate (IP3)-sensitive stores. Activation of both the kinase and the lipase pathways was required for eliciting the Ca2+ response. However, the majority of the [Ca2+]i increase was derived from sources activated by NAD metabolites. Cyclic ADP-ribose (cADPR) evoked Ca2+ release from intracellular stores, and ADPR evoked Ca2+ influx via a nimodipine-sensitive channel. Thus, a multistep cascade couples CCR5 activation to Ca2+ increases in human microglia. Because changes in [Ca2+]i affect chemotaxis, secretion, and gene expression, pharmacol. modulation of this pathway may alter inflammatory and degenerative processes in the CNS.

REFERENCE COUNT: 97 THERE ARE 97 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:503404 CAPLUS

DOCUMENT NUMBER: 145:333423

TITLE: Role of CD38 in airway function

AUTHOR(S): Kang, Bit Na; Guedes, Alonso G. P.; Tirumurugaan, K. G.; Jude, Joseph A.; Deshpande, Deepak A.; Panettieri, Reynold A.; Amrani, Yassine; Lund, Frances E.; Walseth, Timothy F.; Kannan, Mathur S.

CORPORATE SOURCE: Department of Veterinary and Biomedical Sciences, University of Minnesota, St. Paul, MN, USA

SOURCE: Current Respiratory Medicine Reviews (2006), 2(2), 143-156
CODEN: CRMRCI; ISSN: 1573-398X

PUBLISHER: Bentham Science Publishers Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. CD38, a 45-kDa cell surface glycoprotein, is involved in the synthesis of the calcium mobilizing second messenger mol. cyclic ADP-ribose. Cyclic ADP-ribose is known to release calcium from the sarcoplasmic reticulum of airway smooth muscle cells. The pharmacol. features of cyclic ADP-ribose-mediated calcium release in airway smooth muscle cells are distinct from those mediated by inositol 1,4,5-trisphosphate and involve activation of ryanodine receptor channels. In airway smooth muscle cells, contractile agonists recruit cyclic ADP-ribose for intracellular calcium release in a receptor- and receptor-subtype-specific fashion. The CD38/cyclic ADP-ribose signaling has a role in airway function, since methacholine-induced airway resistance is significantly lower in CD38 deficient mice than in the wild type controls. The diminished airway responsiveness appears to result from lower intracellular calcium responses to spasmogens. In human airway smooth muscle cells, inflammatory and Th-2 cytokines increase the expression of CD38 and augment the capacity for cyclic ADP-ribose-mediated calcium release during agonist stimulation. These results suggest a role for cyclic ADP-ribose in airway smooth muscle hyperresponsiveness during inflammation. This review will focus on the role of CD38 and cyclic ADP-ribose in normal airway function and its potential contribution to airway hyperresponsiveness in inflammatory diseases such as asthma.

REFERENCE COUNT: 130 THERE ARE 130 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:259650 CAPLUS

DOCUMENT NUMBER: 142:291376
TITLE: Extracellular NAD+ and cyclic adenosine diphosphate ribose (cADPR) as potent antiinflammatory agents
INVENTOR(S): Fink, Mitchell P.; Delude, Russell L.; Han, Xianonan
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 18 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005065109	A1	20050324	US 2003-659063	20030910
PRIORITY APPLN. INFO.:			US 2003-659063	20030910

AB A method of prophylaxis or treatment of inflammatory conditions, including, but not limited to, intestinal epithelial inflammation due to intestine-specific conditions (e.g., Crohn's disease or ulcerative colitis) or systemic causes of inflammation (e.g., endotoxemia, sepsis, hemorrhagic shock/resuscitation or pancreatitis) is disclosed. In the method, an affected patient is administered a therapeutically effective amount of a composition including an NAD-related compound, in a form that is accessible to a receptor mol., conveyed in a pharmaceutically acceptable carrier vehicle. NAD-related compds. include NAD (NAD+), cyclic ADP ribose (cADPR), or functionally equivalent analogs, derivs., metabolites or agonists thereof, or prodrugs therefor. Also disclosed are ex vivo and in vivo assay methods to test candidate compds. for activity, kits for carrying out the therapeutic methods or the assay methods of the invention and articles of manufacture that include compns. for use in the methods of the invention and instructions for the use thereof.

L3 ANSWER 9 OF 30 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:608702 CAPLUS
DOCUMENT NUMBER: 141:205426
TITLE: Tumor necrosis factor-α differentially regulates the expression of proinflammatory genes in human airway smooth muscle cells by activation of interferon-β-dependent CD38 pathway
AUTHOR(S): Tliba, Omar; Panettieri, Reynold A., Jr.; Tliba, Samira; Walseth, Timothy F.; Amrani, Yassine
CORPORATE SOURCE: Pulmonary, Allergy, and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, Philadelphia, PA, USA
SOURCE: Molecular Pharmacology (2004), 66(2), 322-329
CODEN: MOPMA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recent evidence suggests that CD38, an ectoenzyme that converts NAD+ to cyclic ADP-ribose (cADPr), may play a role in cytokine-induced airway smooth muscle (ASM) cell hyper-responsiveness, a key feature associated with chronic asthma. In the present study, the authors investigated the major signaling pathways by which tumor necrosis factor-α (TNFα) induces CD38 expression and its role in regulating gene expression in human ASM cells. Using flow cytometry analyses, TNFα enhanced CD38 expression in a manner that was time- (0-24 h), concentration- (0.1-40 ng/mL), and protein synthesis- (cycloheximide blockade) dependent. A selective agonistic antibody against tumor necrosis factor receptor (TNFR) 1 also augmented CD38 expression, whereas anti-TNFR2 antagonistic antibody did not prevent the TNFα response. Inhibition of the Janus activated kinase/signal transducer and activator of transcription pathways using the

soluble inhibitor 2-(1,1-dimethylethyl)-9-fluoro-3,6-dihydro-7H-benz-[h]imidaz[4,5-f]isoquinolin-7-one (DBI) or with neutralizing antibody against interferon β (IFNβ) completely abrogated TNFα-induced CD38 expression at both protein and mRNA levels. Combining TNFα (0.1 and 1 ng/mL) and IFNβ (100 IU/mL) at concns. alone that had little effect on CD38 expression induced a robust synergistic induction of CD38 mRNA and protein levels. 8-Bromo-cADPr, a cADPr antagonist, significantly augmented TNFα-induced interleukin-6 secretion, whereas regulated on activation normal T cell expressed and secreted secretion was suppressed. 8-Bromo-cADPr, however, did not affect TNFα-induced cell surface expression of intercellular adhesion mol.-1. The authors' study is the first to demonstrate that IFNβ-dependent activation of CD38 pathway is a novel component by which TNFα differentially regulates the expression of inflammatory genes in ASM cells.

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 1 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:33420 CAPLUS
DOCUMENT NUMBER: 144:106359
TITLE: IL-4 inhibits calcium transients in bovine trachealis cells by a ryanodine receptor dependent mechanism
AUTHOR(S): Ethier, Michael F.; Madison, J. Mark
CORPORATE SOURCE: Department of Medicine, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: FASEB Journal (2006), 20(1), 154-156, 10.1096/fj.05-4031fje
CODEN: FAJOEC; ISSN: 0892-6638
PUBLISHER: Federation of American Societies for Experimental Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB IL-4 and IL-13 have important roles in the pathogenesis of asthma . A novel finding was that brief exposure of airway smooth muscle cells to IL-4 inhibited carbachol-stimulated calcium transients. The authors hypothesized that IL-4 inhibits transients by decreasing calcium store content and tested this by measuring the effects of IL-4 on transients induced by a nonspecific ionophore. Bovine trachealis cells were loaded with fura 2-AM, and cytosolic calcium concns. ([Ca2+]i) were measured in single cells by digital microscopy. Stimulation (SI) with carbachol (10 μM) caused rapid, transient increases in [Ca2+]i to 1299 355 nM. After recovery of calcium stores, stimulation (S2) of the same cells with ionomycin (10 μM), in the absence of extracellular calcium, also increased [Ca2+]i to give S2/S1 ratio of 1.03. However, after 20 min of IL-4 (50 ng/mL), but not IL-13, ionomycin transients were decreased to 0.50 (S2/S1). IL-4 did not inhibit transients with ryanodine receptor calcium release channels (RyR) blocked by ryanodine (200 μM) (S2/S1=1.01) but still did in the presence of 8-bromo cyclic ADP-ribose, an antagonist of cyclic ADP-ribose (cADPR) signaling at RyR (S2/S1=0.48). Together, findings suggest that IL-4 decreases intracellular calcium stores by mechanisms dependent on RyR, but not on cADPR signaling.
REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:644853 CAPLUS
DOCUMENT NUMBER: 142:212750
TITLE: Methodologic advancements in the study of airway smooth muscle
AUTHOR(S): Kotlikoff, Michael I.; Kannan, Mathur S.; Solway, Julian; Deng, Ke-Yu; Deshpande, Deepak A.; Dowell, Maria; Feldman, Morris; Green, Kai Su; Ji, Guangju; Johnston, Robyn; Lakser, Oren; Lee, Jane; Lund, Frances E.; Milla, Carlos; Mitchell, Richard W.; Nakai, Junichi; Rishniw, Mark; Walseth, Timothy F.; White, Thomas A.; Wilson, Jason; Xin, Hong-Bo; Woodruff, Prescott G.
CORPORATE SOURCE: Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY, USA
SOURCE: Journal of Allergy and Clinical Immunology (2004), 114(2, Suppl.), S18-S31
CODEN: JACIBY; ISSN: 0091-6749
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. The study of isolated airway myocytes has provided important information relative to specific processes that regulate contraction, proliferation, and synthetic properties of airway smooth muscle (ASM). To place this information in physiol. context, however, improved methods to

examine airway biol. in vivo are needed. Advances in genetic, biochem., and optical methods provide unprecedented opportunities to improve our understanding of in vivo physiol. and pathophysiol. This article describes 4 important methodol. advances in the study of ASM: (1) the development of transgenic mice that could be used to investigate ASM proliferation and phenotype switching during the development of hypersensitivity, and to investigate excitation-contraction coupling; (2) the use of CD38-deficient mice to confirm the role of CD38-dependent, cyclic ADP-ribose-mediated calcium release in airway responsiveness; (3) investigation of the role of actin filament length and p38 mitogen-activated protein kinase activity in regulating the mech. plasticity-elasticity balance in contracted ASM; and (d) the use of bronchial biopsies to study ASM structure and phenotype in respiratory science.

REFERENCE COUNT: 96 THERE ARE 96 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:556028 CAPLUS

DOCUMENT NUMBER: 141:241927

TITLE: Modulation of calcium signaling by interleukin-13 in human airway smooth muscle: Role of CD38/cyclic adenosine diphosphate ribose pathway

AUTHOR(S): Deshpande, Deepak A.; Dogan, Soner; Walseth, Timothy F.; Miller, Steven M.; Amrani, Yassine; Panettieri, Reynold A.; Kannan, Mathur S.

CORPORATE SOURCE: Departments of Veterinary PathoBiology and Pharmacology, University of Minnesota, St. Paul, MN, USA

SOURCE: American Journal of Respiratory Cell and Molecular Biology (2004), 31(1), 36-42
CODEN: AJRBEL; ISSN: 1044-1549

PUBLISHER: American Thoracic Society

DOCUMENT TYPE: Journal

LANGUAGE: English

AB CD38/cyclic ADP ribose (cADPR) signaling plays an important role in the regulation of intracellular calcium responses to agonists in a variety of cells, including airway smooth muscle (ASM) cells. The present study was aimed at determining the effect of interleukin (IL)-13, a cytokine implicated in the pathogenesis of asthma, on CD38/cADPR signaling and to ascertain the contribution of CD38/cADPR signaling to IL-13-induced airway hyperresponsiveness. Human ASM cells maintained in culture were exposed to 50 ng/mL IL-13 for 22 h and levels of CD38 expression and intracellular calcium responses to agonists were measured. Treatment of human ASM cells with IL-13 resulted in increased CD38 expression as determined by real-time polymerase chain reaction, Western blot anal., and indirect immunofluorescence. Increased CD38 expression was reflected as increased ADP-ribosyl cyclase activity in the ASM cell membranes. The net intracellular calcium responses to bradykinin, thrombin, and histamine were significantly higher in cells treated with IL-13 compared with controls. Furthermore, 8-bromo-cADPR, a cADPR antagonist, attenuated IL-13-induced augmented intracellular calcium responses to agonists in human ASM cells. These findings indicate that the CD38/cADPR-dependent pathway has a major role in IL-13-induced modulation of calcium signaling in human ASM.

REFERENCE COUNT: 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:406899 CAPLUS

DOCUMENT NUMBER: 141:69063

TITLE: Bronchial hyperresponsiveness: insights into new signaling molecules

AUTHOR(S): Amrani, Yassine; Tliba, Omar; Deshpande, Deepak A.; Walseth, Timothy F.; Kannan, Mathur S.; Panettieri, Reynold A.

CORPORATE SOURCE: Department of Medicine, Allergy and Critical Care Division, Pulmonary, University of Pennsylvania Medical Center, Philadelphia, PA, 19104, USA

SOURCE: Current Opinion in Pharmacology (2004), 4(3), 230-234
CODEN: COPUBK; ISSN: 1471-4892

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Signaling mols. play a critical role in the pathophysiol. of airway diseases. Recent evidence shows that cyclic ADP-ribose (cADPr), an endogenous activator of the ryanodine receptor channel in mammalian cells, modulates agonist-induced calcium responses in airway smooth muscle (ASM) cells. In addition, cADPr-mediated calcium release appears to play an important role in the non-specific' increased ASM responsiveness to contractile agonists in cytokine-treated cells, a characteristic finding of asthma. Furthermore, other signaling mols. such as Rho/Rho kinase and phosphodiesterase also contribute to bronchial hyperresponsiveness. Thus, a better understanding of these signaling mols. that alter calcium signaling and contractility of ASM might provide new insight into novel therapeutic targets for the control of bronchial hyperresponsiveness.

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 5 OF 8 MEDLINE on STN

ACCESSION NUMBER: 2006007782 MEDLINE

DOCUMENT NUMBER: PubMed ID: 16280365

TITLE: IL-4 inhibits calcium transients in bovine trachealis cells by a ryanodine receptor-dependent mechanism.

AUTHOR: Ethier Michael F; Madison J Mark

CORPORATE SOURCE: Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.

CONTRACT NUMBER: HL-54143 (NHLBI)

SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (2006 Jan) Vol. 20, No. 1, pp. 154-6. Electronic Publication: 2005-11-09.
Journal code: 8804484. E-ISSN: 1530-6860.

PUB. COUNTRY: United States

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, N.I.H., EXTRAMURAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200603

ENTRY DATE: Entered STN: 6 Jan 2006
Last Updated on STN: 24 Mar 2006
Entered Medline: 23 Mar 2006

AB IL-4 and IL-13 have important roles in the pathogenesis of asthma . A novel finding was that brief exposure of airway smooth muscle cells to IL-4 inhibited carbachol-stimulated calcium transients. We hypothesized that IL-4 inhibits transients by decreasing calcium store content and tested this by measuring the effects of IL-4 on transients induced by a nonspecific ionophore. Bovine trachealis cells were loaded with fura 2-AM, and cytosolic calcium concentrations ([Ca2+]i) were measured in single cells by digital microscopy. Stimulation (S1) with carbachol (10 microM) caused rapid, transient increases in [Ca2+]i to 1299 +/- 355 nM (n=5). After recovery of calcium stores, stimulation (S2) of the same cells with ionomycin (10 microM), in the absence of extracellular calcium, also increased [Ca2+]i to give S2/S1 ratio of 1.03 +/- 0.29. However, after 20 min of IL-4 (50 ng/ml), but not IL-13, ionomycin transients were decreased to 0.50 +/- 0.16 (S2/S1, P=0.02, n=6). IL-4 did

not inhibit transients with ryanodine receptor calcium release channels (RyR) blocked by ryanodine (200 microM) (S2/S1=1.01+/-0.11) but still did in the presence of 8-bromo cyclic ADP-ribose, an antagonist of cyclic ADP-ribose (cADPR) signaling at RyR (S2/S1=0.48+/-0.13). Together, findings suggest that IL-4 decreases intracellular calcium stores by mechanisms dependent on RyR, but not on cADPR signaling.

L5 ANSWER 6 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2004433005 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15309016
TITLE: Methodologic advancements in the study of airway smooth muscle.
AUTHOR: Kotlikoff Michael I; Kannan Mathur S; Solway Julian; Deng Ke-Yu; Deshpande Deepak A; Dowell Maria; Feldman Morris; Green Kai Su; Ji Guangju; Johnston Robyn; Lakser Oren; Lee Jane; Lund Frances E; Milla Carlos; Mitchell Richard W; Nakai Junichi; Rishniw Mark; Walseth Timothy F; White Thomas A; Wilson Jason; Xin Hong-Bo; Woodruff Prescott G
CORPORATE SOURCE: Department of Biomedical Sciences, College of Veterinary Medicine, Cornell University, Ithaca, NY 14853, USA.. mik7@cornell.edu
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AB The study of isolated airway myocytes has provided important information relative to specific processes that regulate contraction, proliferation, and synthetic properties of airway smooth muscle (ASM). To place this information in physiological context, however, improved methods to examine airway biology in vivo are needed. Advances in genetic, biochemical, and optical methods provide unprecedented opportunities to improve our understanding of in vivo physiology and pathophysiology. This article describes 4 important methodologic advances in the study of ASM: (1) the development of transgenic mice that could be used to investigate ASM proliferation and phenotype switching during the development of hypersensitivity, and to investigate excitation-contraction coupling; (2) the use of CD38-deficient mice to confirm the role of CD38-dependent, cyclic adenosine diphosphate-ribose-mediated calcium release in airway responsiveness; (3) investigation of the role of actin filament length and p38 mitogen-activated protein kinase activity in regulating the mechanical plasticity-elasticity balance in contracted ASM; and (d) the use of bronchial biopsies to study ASM structure and phenotype in respiratory science.

L5 ANSWER 7 OF 8 MEDLINE on STN
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TITLE: Modulation of calcium signaling by interleukin-13 in human airway smooth muscle: role of CD38/cyclic adenosine diphosphate ribose pathway.
AUTHOR: Deshpande Deepak A; Dogan Soner; Walseth Timothy F; Miller Steven M; Amrani Yassine; Panettieri Reynold A; Kannan Mathur S
CORPORATE SOURCE: Department of Veterinary PathoBiology, University of Minnesota, St. Paul, MN, USA.
CONTRACT NUMBER: DA11806 (NIDA)
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AB CD38/cyclic adenosine diphosphate ribose (cADPR) signaling plays an important role in the regulation of intracellular calcium responses to agonists in a variety of cells, including airway smooth muscle (ASM) cells. The present study was aimed at determining the effect of interleukin (IL)-13, a cytokine implicated in the pathogenesis of asthma, on CD38/cADPR signaling and to ascertain the contribution of CD38/cADPR signaling to IL-13-induced airway hyperresponsiveness. Human ASM cells maintained in culture were exposed to 50 ng/ml IL-13 for 22 h and levels of CD38 expression and intracellular calcium responses to agonists were measured. Treatment of human ASM cells with IL-13 resulted in increased CD38 expression as determined by real-time polymerase chain reaction, Western blot analysis, and indirect immunofluorescence. Increased CD38 expression was reflected as increased ADP-ribosyl cyclase activity in the ASM cell membranes. The net intracellular calcium responses to bradykinin, thrombin, and histamine were significantly ($P \leq 0.05$) higher in cells treated with IL-13 compared with controls. Furthermore, 8-bromo-cADPR, a cADPR antagonist, attenuated IL-13-induced augmented intracellular calcium responses to agonists in human ASM cells. These findings indicate that the CD38/cADPR-dependent pathway has a major role in IL-13-induced modulation of calcium signaling in human ASM.

L5 ANSWER 8 OF 8 MEDLINE on STN
ACCESSION NUMBER: 2004241782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 15140413
TITLE: Bronchial hyperresponsiveness: insights into new signaling molecules.
AUTHOR: Amrani Yassine; Tliba Omar; Deshpande Deepak A; Walseth Timothy F; Kannan Mathur S; Panettieri Reynold A Jr
CORPORATE SOURCE: Pulmonary, Allergy and Critical Care Division, Department of Medicine, University of Pennsylvania Medical Center, BRB II/III, 421 Curie Boulevard, Philadelphia, PA 19104, USA.. amrani@mail.med.upenn.edu
CONTRACT NUMBER: 1P50 HL 67663 (NHLBI)
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pp. 230-4. Ref: 44
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AB Signaling molecules play a critical role in the pathophysiology of airway diseases. Recent evidence shows that cyclic ADP-ribose (cADPr), an endogenous activator of the ryanodine receptor channel in mammalian cells, modulates agonist-induced calcium responses in airway smooth muscle (ASM) cells. In addition, cADPr-mediated calcium release appears to play an important role in the "non-specific" increased ASM responsiveness to contractile agonists in cytokine-treated cells, a characteristic finding of asthma. Furthermore, other signaling molecules such as Rho/Rho kinase and phosphodiesterase also contribute to bronchial hyperresponsiveness. Thus, a better understanding of these signaling molecules that alter calcium signaling and contractility of ASM might provide new insight into novel therapeutic targets for the control of bronchial hyperresponsiveness.